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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,042	11/21/2000	Nathaniel Hunt	3367	2319

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EXAMINER

ZEMAN, MARY K

ART UNIT	PAPER NUMBER
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1631

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DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/721,042

Applicant(s)

HUNT, NATHANIEL

Examiner

Mary K Zeman

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 April 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-59 is/are pending in the application.
- 4a) Of the above claim(s) 16-44 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 and 45-59 is/are rejected.
- 7) ☒ Claim(s) 4 and 5 is/are objected to.
- 8) ☒ Claim(s) 1-59 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *Notice to comply*.

Art Unit: 1631

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I claims 1-15 and 45-59 in Paper No. 4 is acknowledged.

Claims 16-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in Paper No. 4.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. The IDS citing two documents has been considered, and a copy is included with this action.

Drawings

Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect may be deferred until after the examiner has considered the proposed drawing correction. Failure to timely submit the proposed drawing correction will result in the abandonment of the application.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Applicant is required to update the status of applications listed in the specification, and to fill in places left blank.

Art Unit: 1631

The disclosure is objected to as it contains polynucleotide sequences that do not contain the required SEQ ID NO. (see at least p. 31-33) The specification also lacks paper copy and computer readable of a sequence listing that comprises each of the polynucleotide sequences. See CFR 1.821 et al.

Failure to comply will render the reply non-responsive.

Claim Objections

Claims 4 and 5 are objected to because of the following informalities: A typographical error "of Claim 3 wherein..." A space is missing between "3" and "wherein". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of claim 1 are unclear, as the method steps set forth in the claim only set forth the selection of a single probe, while the preamble of the claim sets forth the selection of multiple probes.

Within claim 2, there is no indication as to what type of data should be used in the equation- to what is the hybridization intensity equation being applied? Further, it appears to require prior knowledge of the sequence of the probe (value S_i), which has not yet been predicted by the method. The specification does not clarify this issue.

Within claim 3, the phrase "a functional of said sequence" is unclear. If Applicant intends "a function of said sequence" which would appear to be grammatically correct, it is still entirely unclear how the sequence of a probe would provide the function (or functional). The specification does not clearly set forth a definition of this term.

Art Unit: 1631

Within claim 4, it is unclear how one is to empirically determine the free energy of a base in a probe sequence which is merely a computer prediction, and is not actually a chemical substance that can be tested. The specification indicates that this value is predicted from previously determined data, however the claim is not so limited.

Within claim 6, on what data is the least squares analysis performed? What does the training set include, and how is it used in the least squares analysis, and how does it affect the equation set forth in claim 2? The specification is not illuminating in this regard.

Similarly within claim 7, to what is the Cholesky decomposition applied, and how is the resulting information used in the equation of claim 2? The specification is not illuminating in this regard.

Within claim 8 it is entirely unclear how the recited step is to affect the equation of claim 2, it is unclear how or what data should be used to generate a smooth function, or even how a smooth function is generated such that it can be used in the equation of claim 2.

Similarly in claim 10, it is entirely unclear how the recited step is to affect the equation of claim 2, it is unclear how or what data should be used to generate a smooth function, or even how a smooth function is generated such that it can be used in the equation of claim 2.

In claims 12-14 it is entirely unclear how or where the additional parameters should be added to the equation of claim 2.

Within claim 15, how is the singular value decomposition applied? To what data? How does it affect the equation of claim 2?

These same problems exist within the software and system claims of 45-59. The claims all fail to specifically set forth the steps which meet the goals of the preamble with appropriate definiteness. The dependent claims fail to specifically set forth how they further limit the original method claims, and where within the method these further limitations should be added or inserted.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Art Unit: 1631

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 45 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 15 and 27 of copending and commonly assigned Application No. 09/718295. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of the instant application encompass the methods of the '295 application. Both methods require the selection of probes through the comparison of hybridization intensities. While the '295 application has additional steps that are not specifically recited in the claims of the instant application, the generic claims encompass those steps as they recite "comprising" and equivalent steps are disclosed in the specification.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Art Unit: 1631

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Hacia et al. (1998).

The claims are drawn to computer-implemented methods for selecting probes based upon predicted hybridization intensities, and computer software products therefor.

Hacia et al. (Hacia, J.G. et al. Genome Research Vol 8 :1245-1258 (1998): PTO-1449) discloses computer implemented methods for selecting probes based upon predicted stability and affinity calculations which represent predicted hybridization affinity. At page 1256, the particular algorithms and equations developed are disclosed, and appear to be minor rearrangements of the equations set forth in claims 2 and 50. This algorithm predicts the potential for duplex formation between adjacent probes within a feature on the array as well as within a given probe (probe-probe interactions, and hairpin interactions). An inter- and intra- molecular probe structure normalization score is used, which takes into account perfect match and control probes, and use one of the four traditional bases as a reference base. A smooth polynomial function is employed to describe and correct for probe sequence composition effects. The correction scheme starts with finding the best least squares fit to the logs of the measured (or predicted) perfect match intensity ratios. The least squares parameters are solved using a Cholesky decomposition. These steps were all done using a computer. To the extent the claims set forth a particular method and/or steps, this disclosure anticipates the claims.

Claims 1 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Lange et al. (USP 6,403,314 B1).

Lange et al. (USP 6,403,314 B1 having a filing date of 2/4/2000) disclose computer implemented methods of selecting probes based upon predicted hybridization. A matrix is generated that represents the ability of various probes to hybridize with the target sequence in comparison with control sequences. The term used by Lange is "stability" which is a factor in predicted hybridization intensity. The algorithms take in to account cross-hybridizations and loop formation (hairpins). The algorithms can employ free energy calculations, or other thermodynamic considerations. As such this disclosure anticipates the rejected claims.

Art Unit: 1631

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 102(e) as being anticipated by Santalucia et al. (WO 01/94611 A2).

Santalucia et al. (WO 01/94611 A2, having a priority date of 7 June 2000) discloses computer implemented methods for selecting probes based upon predicted hybridization between probe and target sequence. The disclosed modules of this reference appear to perform the same calculations as those recited in claims 2 and 50, however the same equations are not listed. To the extent the claims set forth a particular method and/or steps, this disclosure anticipates the claims.

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 102(e) as being anticipated by Shannon et al. (US 6,251,588 B1).

Shannon et al. (USP 6,251,588 B1 having priority to 2/10/1998) disclose methods of predicting the potential of an oligonucleotide to hybridize to a target sequence. Various parameters relating to the ability of a given sequence to hybridize to another are calculated and compared to other sequences, such as control sequences. These parameters are indicative of a predicted hybridization intensity. Table 1 sets forth the various algorithms employed, and they include the intramolecular partition function which is recited in a slightly rearranged form in claims 2 and 50. Various free energy equations are set forth, as well as equations to analyze probe-probe interactions, hairpin interactions sequence complexity, steric factors, etc. As such this disclosure meets the limitations of the claims.

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolber et al. (US 6,461,816 B1).

Wolber et al. (USP 6,461,816 B1 having priority to 9 July 1999) disclose methods of predicting the potential of an oligonucleotide to hybridize to a target sequence. Various parameters relating to the ability of a given sequence to hybridize to another are calculated and compared to other sequences, such as control sequences. These parameters are indicative of a predicted hybridization intensity. The specification sets forth the various algorithms employed, and they include the intramolecular partition function which is recited in a slightly rearranged form in claims 2 and 50. Various free energy equations are set forth, as well as equations to

Art Unit: 1631

analyze probe-probe interactions, hairpin interactions sequence complexity, steric factors, etc.

As such this disclosure meets the limitations of the claims.

Claims 1 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Hyndman et al. (1996)

Hyndman et al. (Hyndman et al. BioTechniques (1996), 20(6), 1090-1094, 1096-1097) disclose computer simulations and predictions of hybridizations between oligonucleotide probes and a target sequence wherein the best probes with the best predicted hybridization are selected. The programs use several free energy calculations and meet the limitations of the rejected claims.

Claims 1 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Schutz et al. (1999).

Schutz et al. (Schutz et al. BioTechniques (1999), 27(6), 1218-1220, 1222, 1224) disclose computer implemented methods of selecting oligonucleotide probes based upon predicted hybridization calculations. Control probes are employed, various free energy calculations are used, and the program can calculate the effects of all possible mutations. As such this disclosure meets the limitations of the rejected claims.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Balaban USP 6,510,391 B1 references the instant application and sets forth the methods of the instant claims in detail.

Mei et al. (WO 02/42485 A2) is the international publication related to US 09/718295.

Hunt (EP 1209612 A2) is the EP publication related to the instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028.


Art Unit: 1631

Official fax numbers for this Art Unit are: (703) 308-4242, (703) 872-9306. An *unofficial* fax number, direct to the Examiner is (703) 746 5279. Please call prior to use of this number.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the TC1600 Receptionist whose telephone number is (703) 308-0196.

mkz

4/18/03



MARY K. ZEMAN
PRIMARY EXAMINER

